

**AWARD NUMBER: W81XWH-16-1-0450**

**TITLE: Multispecies, Integrative GWAS for Focal Segmental Glomerulosclerosis**

**PRINCIPAL INVESTIGATOR: Ali G. Gharavi**

**RECIPIENT: Columbia University Medical Center  
New York, NY 10032-3702**

**REPORT DATE: September 2018**

**TYPE OF REPORT: Annual**

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Fort Detrick, Maryland 21702-5012**

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<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> The goal of this project are to identify genetic determinants of focal segmental glomerulosclerosis (FSGS) using genomewide association studies in mouse strains. We have shown that the development nephropathy in the HIV-1 transgenic mice(TgFVB) is highly strain dependent. Linkage mapping in murine crosses have shown that there are at least 4 FSGS susceptibility loci among inbred strains. Furthermore, F1 hybrids between TgFVB and other inbred strains show highly variable penetrance of nephropathy, indicating the feasibility of mapping genes using F1 hybrids for association mapping. In the past funding periods, we have generated 459 F1 hybrids between TgFVB and 15 inbred strains and have determined variable susceptibility to kidney disease based on genetic background, with C57Bl6/J, A/J, DBA/1J, NZO/HILtJ, C3H/HeJ and CBA/J mice showing highest prevalence of injury as measured by proteinuria, and urinary NGAL levels. The increased prevalence of pathology, measured by glomerulosclerosis, was observed on the WSB/EiJ, CBA/J, DBA/1J, C3H/HeJ, and A/J genetic backgrounds. By performing serial analysis of proteinuria, we have also determined the optimal timepoint for assessment of kidney disease in the f1 progeny. Our goal is continue breeding the F1 cohort using total of 30 inbred strains We will continue to characterize phenotypes based on proteinuria, UNGAL and histopathology. Once the cohort has been generated, we will perform a GWAS to detect susceptibility loci for FSGS and compare results to the ongoing GWAS in humans.					
<b>15. SUBJECT TERMS</b> None listed					
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## 1. INTRODUCTION:

The glomerular filtration barrier amongst mammals is highly conserved, and mouse models are highly relevant to understanding the human pathogenesis of FSGS. Frequently candidate genes identified in mouse models have been implicated in the cause of human disease, demonstrating the importance of genes identified in the mouse FSGS model are highly relevant to human disease. The development of nephropathy in HIV-1 transgenic mice are highly strain dependent, breeding these mice on to diversity out cross mice strains will enable us to preform GWAS for FSGS in mice to identify new genes.

## 2. KEYWORDS:

FSGS, GWAS, Nephropathy, Mouse, Kidney disease

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

### **What were the major goals of the project?**

*List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.*

Generate 1,250 HIV-1 transgenic F1 hybrids between TgFVB and other inbred and outbred strains of mice.

Preform detailed assessment of severity of kidney disease based on histopathology, proteinuria, urine NGAL production at 6 weeks of age.

Preform genome-wide genotyping and quantitative GWAS for FSGS in mice.

### **What was accomplished under these goals?**

*For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant*

results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

We are currently generating transgenic F1 hybrids between the TgFVB and 30 inbred strains of mice, characterizing the phenotypes based on proteinuria, urine NGAL and histopathology. Following collection of the urine the level of proteinuria, hematuria and NGAL (UNGAL) is determined in the Tg-F1 hybrids. Upon euthanasia of the mice, kidneys are prepared for histopathologic analysis and for RNA extraction, serum has been collected and stored in three vials for metabolic and immunological analysis, the urine, spleen and feces are collected and bio-banked at this time point. UNGAL is measured in urine, before and at the time of proteinuria detection in the Tg-F1 mice. Kidney sections for histopathology have been processed and stained with Periodic acid–Schiff (PAS). Currently 381 slides have been read and analyzed in the Pathology division and an additional 72 slides will be processed by the end of September – mid October 2018.

Currently in 15 strains of mice we have completed the pathology (% glomerulosclerosis (GS), % Casts, % tubular atrophy and fibrosis, % interstitial inflammation), urine analysis (NGAL, proteinuria, and hematuria) and serum analysis (BUN, IgA and IgG). Our data has demonstrated, that not all the Tg-F1 hybrids develop proteinuria (Table 1). The Tg-F1 hybrids derived from the A/J, C3H/HeJ, C57BL/6J, CBA/J, DBA/1J and NZO/HILtJ mice had increased numbers of Tg-mice positive for proteinuria compared to the Tg-F1 hybrids generated from the other strains of mice.

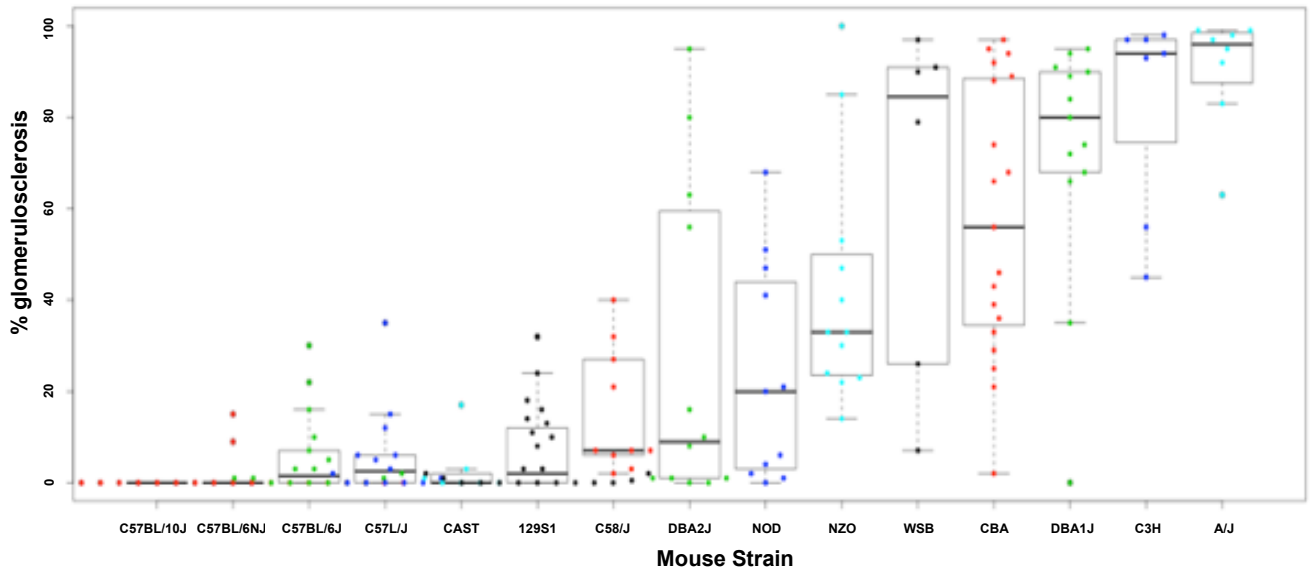
**Table 1:** Phenotypic characterization of the Tg-F1 hybrids derived from different mouse strains.

F1-hybrid	# pups	Male	Female	Transgene	M-Transgene (% proteinuria)	F-Transgene (% proteinuria)	GS > 10% (% Tg-mice)
129S1/SvimJ	36	19	17	24	11 (27%)	13 (46%)	8 (33%)
A/J	23	11	12	8	3 (100%)	5 (100%)	8 (100%)
C3H/HeJ	15	5	10	7	4 (100%)	3 (100%)	7 (100%)
C57BL10/J	26	14	12	11	6 (0%)	5 (0%)	0 (0%)
C57BL/6J	44	18	26	18	8 (50%)	10 (50%)	4 (22%)
C57BL/6NJ	32	15	17	20	9 (0%)	11 (0%)	1 (5%)
C57L/J	34	13	21	17	6 (50%)	11 (27%)	5 (29%)
C58/J	16	10	6	10	5 (40%)	5 (60%)	4 (40%)
CAST/EiJ	10	3	7	7	1 (0%)	6 (50%)	1 (14%)
CBA/J	27	14	13	18	10 (70%)	8 (50%)	18 (94%)
DBA/1J	27	14	13	14	5 (80%)	9 (88%)	13 (92%)
DBA/2J	32	13	19	12	7 (28%)	5 (40%)	12 (50%)
NOD/ShiLt	30	17	13	11	6 (33%)	5 (20%)	6 (55%)
NZO/HILtJ	24	12	12	12	6 (100%)	6 (80%)	12 (100%)
WSB/EiJ	11	5	6	6	1 (100%)	5 (60%)	5 (84%)
BALB/C*	51	In-progress	In-progress	In-progress	In-progress	In-progress	In-progress
C3H/HeJ*	21	In-progress	In-progress	In-progress	In-progress	In-progress	In-progress

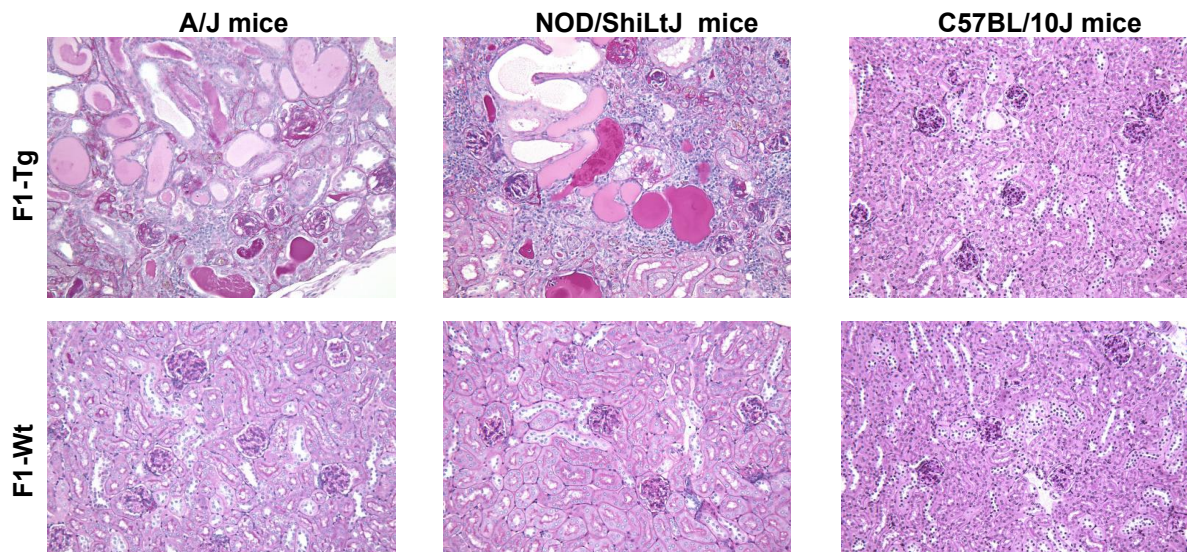
Differences in the pathologies of the generated Tg-F1 hybrids pathologies were seen, presented by the amount of glomerulosclerosis (Figure 1). Three stains (A/J, C3H/HeJ, and DBA/1J) were highly sensitive to the Tg resulting in severe glomerulosclerosis.

6 strains (129S1/SvImJ, C57BL/10J, C57BL/6J, C57BL/6NJ, C57L/J, and CAST/EiJ) were resistant to the Tg resulting in limited to no glomerulosclerosis, and 6 strains (C58/J, CBA/J, DBA/2J, NOD/ShiLtJ, NZO/HILtJ and WSB/EiJ) had intermediate glomerulosclerosis. Representative pathology is shown for mice with severe glomerulosclerosis (A/J mice Figure 2) and no glomerulosclerosis (C57BL/10J mice Figure 2). The glomerulosclerosis score correlated with the presence of casts, interstitial fibrosis and tubular atrophy, interstitial inflammation, proteinuria, elevated plasma BUN, and decreased plasma IgG concentrations. There is a correlation between the elevated levels of BUN and the increased amount of glomerulosclerosis in the Tg-F1 hybrid mice (Figure 3). There was no kidney pathology in the wildtype F1 hybrid mice.

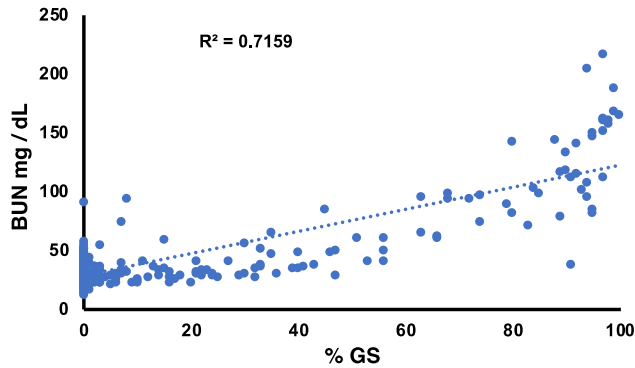
**Figure 1:** The range of glomerulosclerosis for each of the Tg-mice strain



**Figure 2:** Periodic acid–Schiff stained histology of F1-A/J mice that highly sensitive to the Tg resulting in severe glomerulosclerosis (Upper left panel), NOD/ShiLtJ intermediate glomerulosclerosis (Upper middle panel) and F1-C57BL/10J mice that are resistant to the transgene resulting in no glomerulosclerosis (Upper right panel). The F1-A/J, F1-NOD/ShiLtJ and F1-C57BL/10J Wt mice are shown in the left, middle and right lower panel respectively.



**Figure 3:** Increase BUN is correlated with severity of glomerulosclerosis



With the increased severity of glomerulosclerosis and the increased BUN measured in the plasma, we noticed decreases in the IgG plasma concentration of these mice.

To determine if there were baseline differences between the 15 wildtype F1 hybrid mice, IgA, IgG and BUN plasma concentrations were determined. Significant differences were observed in the BUN (ANOVA p-value < 0.001), IgG (ANOVA p-value < 0.001), and highly significant differences were observed in plasma IgA (ANOVA p-value < 0.001), between the groups of mice.

We are currently adding additional inbred strains of mice to this study.

**What opportunities for training and professional development has the project provided?**

*If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. “Training” activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. “Professional development” activities result in increased knowledge or skill in one’s area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.*

This award provides additional training to Dr. Steers, an Associate Research Scientist in my lab to utilize and learn additional skill sets.

Results generated in association with this award will be presented at conferences, seminars and research meetings by Dr. Steers.

This award provides training for post-bac students and summer students who are currently working in the laboratory who intend to go on the graduate education.

**How were the results disseminated to communities of interest?**

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.*

We will be presenting the data at the American Society of Nephrology 2018 meeting.

Poster Presentation ‘Inter-strain variation in severity of nephropathy and immunoglobulin levels in HIV-1 transgenic mice’

**What do you plan to do during the next reporting period to accomplish the goals?**

*If this is the final report, state “Nothing to Report.”*

*Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.*

We will continue to breed and generating transgenic F1 hybrids between the TgFVB and the diversity outcross mice. The kidneys, serum, urine, spleen and feces will be collected and bio-banked.

Urine will be collected and analyzed for proteinuria, hematuria and NGAL for the phenotypic analysis of the newly generated transgenic F1 hybrids.

Serum will be analyzed for blood urea nitrogen, albumin, cholesterol levels, immunological and inflammatory markers for the phenotypic analysis.

We will perform an interim GWAS with 15 strains to detect potential associations with nephropathy traits. We will perform the full GWAS once F1 hybrids with all 30 strains have been generated.

- 4. IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

**What was the impact on the development of the principal discipline(s) of the project?**

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).*

The study will use novel methods to find new genes involved in kidney diseases and the pathogenesis of HIV associated nephropathy.

**What was the impact on other disciplines?**

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.*

The study will use novel methods to find new genes involved in kidney diseases and the pathogenesis of HIV associated nephropathy.

**What was the impact on technology transfer?**

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:*

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report

**What was the impact on society beyond science and technology?**

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:*

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report

- 5. CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

**Changes in approach and reasons for change**

*Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.*

Nothing to Report

**Actual or anticipated problems or delays and actions or plans to resolve them**

*Describe problems or delays encountered during the reporting period and actions or plans to resolve them.*

Nothing to Report

**Changes that had a significant impact on expenditures**

*Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.*

Nothing to Report

**Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

*Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.*

**Significant changes in use or care of human subjects**

Nothing to Report
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**Significant changes in use or care of vertebrate animals.**

Nothing to Report
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**Significant changes in use of biohazards and/or select agents**

Nothing to Report
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6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state “Nothing to Report.”

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

**Journal publications.** *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume; year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report

**Books or other non-periodical, one-time publications.** *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report

**Other publications, conference papers, and presentations.** *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (\*) if presentation produced a manuscript.*

Data pertaining to this project is periodically presented in Laboratory meetings.

We will be presenting the data at the American Society of Nephrology 2018 meeting.  
Poster Presentation 'Inter-strain variation in severity of nephropathy and immunoglobulin levels in HIV-1 transgenic mice'

- **Website(s) or other Internet site(s)**

*List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.*

Nothing to Report

- **Technologies or techniques**

*Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.*

Nothing to Report

- **Inventions, patent applications, and/or licenses**

*Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.*

Nothing to Report

- **Other Products**

*Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:*

- *data or databases;*
- *biospecimen collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to Report

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

### **What individuals have worked on the project?**

*Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change.”*

Example:

Name: *Mary Smith*  
Project Role: *Graduate Student*  
Researcher Identifier (e.g. ORCID ID): *1234567*  
Nearest person month worked: *5*

Contribution to Project: *Ms. Smith has performed work in the area of combined error-control and constrained coding.*  
Funding Support: *The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name: Ali Gharavi  
Project Role: Principal Investigator  
Researcher Identifier (e.g. ORCID ID): N/A  
Nearest person month worked: 1.2

Contribution to Project: Dr. Gharavi was responsible for achieving the overall goals of the study. He supervised mouse genetic studies at Columbia University and will collaborate with Dr. Sanna-Cherchi (partnering PI) on the human genetic studies.

Funding Support: Dr. Gharavi's funding portfolio currently includes NIH Grants 5UM1DK100876-04, NIH 5R01MD009223-03, 5R01DK082753-07, 5U54DK104309-03, 5U01HG008680-02, 2R01DK080099-06A1, 1R21DK109690-01 and 1UG3OD231183-01 and USAMRAA Grant PR151419.

Name: Iulina Ionita-Laza  
Project Role: Co- Investigator  
Researcher Identifier (e.g. ORCID ID): N/A  
Nearest person month worked: .22

Contribution to Project: sequencing data, analysis of datasets GWAS

Funding Support: Dr. Ionita-Laza's funding portfolio currently includes NIH Grants 5R01MH095797-04, 5R21MH106888-02, 5R01MH106910-02, 5R01HG008980-02, 5R01AR065963-03, 1P50AR070588-01, 5R01DK080099-07, USAMRAA Grant PR151419.

Name: Vivette D'Agati  
Project Role: Co-Investigator  
Researcher Identifier (e.g. ORCID ID): N/A  
Nearest person month worked: .84

Contribution to Project: Dr. D'Agati perform standardized review and scoring of kidney biopsies for enrolled patients and mouse samples.

Funding Support: Dr. Agati's funding portfolio currently includes NIH Grants 1 UM1 DK100876-01, 1R01MD009223-01, 1R24DK103032-01, 1R01DK106436-01A1 USAMRAA Grant PR151419.

Name: Nicholas Steers  
Project Role: Associate Research Scientist  
Researcher Identifier (e.g. ORCID ID): N/A  
Nearest person month worked: 9.0

Contribution to Project: Dr. Steers performed the GWAS in the TgFVBxDO F1 mice, under the supervision of Dr. Ionita-Laza and Dr. Gharavi.

Funding Support: N/A

Name: Wan Yee Lam  
Project Role: Tech  
Researcher Identifier (e.g. ORCID ID): N/A  
Nearest person month worked: 6.0

Contribution to Project: Wet lab experiments, DNA preparation and plating. Processed mouse husbandry and genotyping and processing samples for histopathology.

Funding Support: N/A

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.*

Nothing to Report

**What other organizations were involved as partners?**

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

- *Nothing to report*

Nothing to Report

**8. SPECIAL REPORTING REQUIREMENTS**

**COLLABORATIVE AWARDS:** For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is

acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.

Dr. Gharavi and Dr. Sanna-Cherchi will submit cognate reports.

**QUAD CHARTS:**

N/A

**9. APPENDICES: N/A**